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(54) Title: NOVEL STEROID NITRITE AND NITRATE ESTER DERIVATIVES USEFUL AS ANTI-INFLAMMATORY DRUGS

(57) Abstract

The present invention relates to a compound having the formula A-B-C, wherein A is a hydroxyl containing steroidal hormone; C is a nitrite or nitrate containing compound; and B is lower alkyl, lower alkenyl, lower alkynyl, and to pharmaceutical compositions thereof. These compounds are anti-inflammatory and vasodilation agents.

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# NOVEL STEROID NITRITE AND NITRATE ESTER DERIVATIVES USEFUL AS ANTI-INFLAMMATORY DRUGS

## Background of the Invention

## Field of the Invention

The present invention relates to novel steroid nitrite/nitrate ester derivatives, and to their use treating inflammatory diseases.

## Related Art

Steroids, specifically of the glucocorticoid class of molecules, are known to possess anti-inflammatory and immunomodulatory activities and are commonly utilized for the treatment of numerous autoimmune and inflammatory diseases. However, their beneficial effects are often slow to develop and accompanied by many dose-limiting side-effects. Nitric oxide donors, such as nitroglycerin, have also been utilized as pharmaceutical agents with prominent beneficial effects on the cardiovascular system. Many of the biological actions of nitric oxide potentially counteract the side-effects of the glucocorticoids and may enhance their therapeutic actions. The present invention relates to novel steroid nitrite/nitrate ester derivatives that possess the combined biological properties of glucocorticoids and nitric oxide donors in a single molecule. These molecules have an advantage over currently utilized glucocorticoids in that they rapidly elicit beneficial pharmacological effects, such as bronchial relaxation, through the release of nitric oxide. It is intended that these novel molecules be utilized for therapy, in particular their use as anti-inflammatory and immunosuppressive drugs for the treatment of rheumatic diseases, immunological disorders, skin disorders, inflammation, transplant rejection, cancer, osteoporosis, rhinitis and asthma with less side-effects.

Glucocorticoids are commonly utilized for the pharmacologic treatment of inflammation and undesirable immune system reactions. These steroids have the capacity to prevent or suppress the development of inflammation resulting from a number of different injurious agents including infectious, immunological, chemical, mechanical, and radiation. Glucocorticoids are also effective in the treatment of immune system disorders including autoimmune diseases such as rheumatoid arthritis and lupus, and transplant rejection. However, the therapeutic applications of these steroids are somewhat limited due to toxicity and side-effects. The major side effects of the glucocorticoids are hypertension, peptic ulcers, increased susceptibility to infections, osteoporosis, hyperglycemia, and vascular occlusion.

It has been known since the early 1980's that the vascular relaxation brought about by acetylcholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years and NO is the active component of amylnitrite ester, glyceryltrinitrate and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid L-arginine by the enzyme nitric oxide synthase. The NO released by the constitutive enzyme acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of

biological actions in addition to endothelium-dependent relaxation including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al. Biochemical Pharmacology, 38, 1709-1715 (1989) and Moncada et al. Pharmacological Reviews, 43, 109-142 (1991). Furthermore, NO has been shown to possess anti-thrombotic (see Moncada et al. Journal of Cardiovascular Pharmacology 17, S25 (1991), Byrne et al., World Patent application WO9403421-A2 and Schonafinger et al., German Patent application DE4223800-A1 ), bronchorelaxant (Persson et al. European Journal of Pharmacology, 249, R7-R8 (1993), anti inflammatory, microbialcidal (Alspaugh and Granger, Infection and Immunity 59, 2291-2296 (1991) and gastroprotective (see Wallace et al. European Journal of Pharmacology, 257, 249-255 (1994) effects in animal models. In addition, nitric oxide has been suggested to be effective against the loss of bone in *in vitro* models of osteoporosis (MacIntyre et al. Proc.Natl.Acad.Sci.USA 88, 2936-2940 (1991) and in inhibiting angiogenesis, tumour growth and metastasis in *in vivo* animal models (Pipili-Synetos et al. British Journal of Pharmacology, 116, 1829-1834 (1995). In United States Patents 3,930,970, 3,298,941 and 3,215,713, a novel photochemical process for the preparation of diol mononitrates from alcohol nitrites is disclosed. In United States Patents 3,639,434, 3,743,741 and 3,839,369, the preparation of steroid nitrate esters and their uses as intermediates is disclosed. In German Patent 1643034, a method for the preparation of steroid nitrate esters is disclosed. In Canadian Patent 975755 and 969927, a process for the preparation and acidolysis of nitrate esters of 21-alcohols of the pregnane series is disclosed, respectively. In British Patent 1,082,573 and 1,082,574, a process for the preparation of steroid-11-nitrate esters and their uses as intermediates is disclosed.

Thus, these properties make nitric oxide an ideal agent to enhance the actions of corticosteroids in the treatment of various diseases mentioned earlier by both increasing their biological effects as well as by reducing their side effects. The present invention relates to novel nitrite/nitrate esters of steroids, processes for their preparation, pharmaceutical compositions containing them, and methods for their use.

## Summary of the Invention

The present invention relates to a pharmaceutical composition or preparation which comprises hydroxyl containing steroidal hormones and organic nitrite/nitrate or other nitric oxide donating agents which can be administered simultaneously, sequentially or separately: Representative examples of hydroxyl containing steroidal hormones known in the art inclose those listed in the Merck Index, Eleventh Edition (1989) as follows (the respective compound numbers are given each):

21-Acetoxypregnenolone, 70

Alclometasone, 213

Algestone, 229

Amcinonide, 398

Beclomethasone, 1029

Betamethasone, 1202

Budesonide, 1455

Chlorprednisone, 2157

Clobetasol, 2361

Clocortolone, 2368

Cloprednol, 2396

Corticosterone, 2532

Cortisone, 2533

Hydrocortisone Phosphate, 4712

Hydrocortisone 21-Sodium Succinate, 4713

Hydrocortisone terbutate, 4714

Maziipredone, 5644

Medrysone, 5679

Meprednisone, 5750

Methylprednisolone, 6028

Mometasone Furoate, 6151

Paramethasone, 6977

Prednicarbate, 7177

Prednisolone 21-Diethylaminoacetate, 7720

Corticazol, 2536

Deflazacort, 2852

Desonide, 2908

Dexamethasone, 2922

Diflorasone, 3126
Diflucortolone, 3129

Difluprednate, 3134

Enoxolone, 3543
Fluazacort,4048
Flucloronide, 4053
Flumethasone, 4066
Flunisolide, 4071

Flucinolone Acetonide, 4076
Fluocinonide, 4077
Fluocortin Butyl, 4078
Fluocortolone, 4079

Fluorometholone, 4104

Fluperolone, Acetate, 4118

Fluprednidene Acetate, 4115
Fluprednisolone, 4119
Flurandrenolide, 4112
Formocortal, 4156
Halcinonide, 4504
Halometasone, 4510
Haloprednone Acetate, 4512
Hydrocortamate, 4709
Hydrocortisone, 4710

Prednisolone Sodium Succinate, 7722

Prednisolone Sodium Phosphate, 7721
Prednisolone Sodium 21-m-Sulfo-benzoate, 7723
Prednisolone 21-Stearoylglycolate, 7724

Prednisolone Terbutate, 7725
Prednisolone 21-Trimethylacetate, 7726

Prednisone, 7727
Prednival, 7728
Prednylidene, 7729
Prednylidene 21-Diethylaminoacetate, 7730

Tixocortol, 9408
Triamcinolone, 9511
Triamcinolone Acetonide, 9512
Triamcinolone Benetonide, 9513
Triamcinolone Hexacetonide, 9514

Not listed in the Merck Index
Fluticasone

Preferred examples are glucocorticoids and synthetic steroidal compounds with glucocorticoid activity. Representative examples of organic nitrites and nitrates or other nitric oxide donating compounds including such as glyceryl nitrate, amylnitrite, isosorbide mononitrate, isosorbide dinitrate, mannitol nitrate, pentaerythritol nitrate, propatyl nitrate and furoxan derivatives;

The present invention further discloses a preferred compound of Formula 1 and pharmaceutically acceptable ester and prodrugs thereof,

**A-B-C** 1

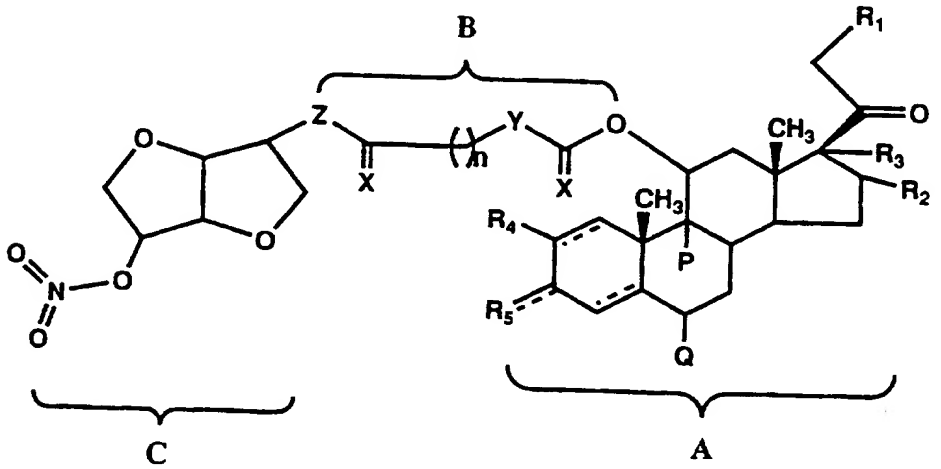
wherein;

**A** is a residue of a hydroxyl containing steroidal hormone. Representative examples of hydroxyl containing steroidal hormones known in the art inclose those listed in the Merck Index, Eleventh Edition (1989) as listed above. Preferred examples are glucocorticoids and synthetic steroidal compounds with glucocorticoid activity.

**B** is a spacer preferably containing a maximum of 12 carbon atoms, connecting **A** through the hydroxyl moeity and **C** through an amino or a hydroxyl group via an amide, ester, carbamate or carbonate linkage.

**C** is an organic nitrite or nitrate compound, or other nitric oxide donating compounds such as furoxan derivatives. Representative examples of organic nitrite or nitrate compounds are glyceryl nitrate, amylnitrite, isosorbide mononitrate, isosorbide dinitrate, mannitol nitrate, pentaerythritol nitrate, propatyl nitrate.

The scope of the compounds of the present invention is defined above by the Formula **A-B-C (I)** and preferreably includes those characterized by the structural formula **II** and **III**, and pharmaceutically acceptable ester and prodrugs thereof,




II

wherein;

the dotted lines in Formula **II** indicate a single or a double bond;

$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$) halogen, thiol, alkylmercapto, heterocycles, lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

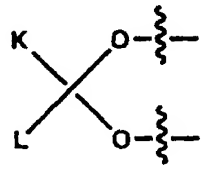
$R_1$ is a group of the formula OCO-$R_6$ wherein $R_6$ is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy group;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), lower alkyl, lower alkenyl, lower

alkynyl, lower alkoxy wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals;or

$R_2$ and $R_3$ are independently selected from the group of formula OCO-$R_7$ wherein $R_7$ is 2-furanyl, lower alkyl or lower alkoxy group,

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl, or optionally K and L can form an alicyclic hydrocarbon ring or heterocyclic ring;

$R_4$ is hydrogen or halogen;

$R_5$ is hydrogen, hydroxyl or oxygen;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group;

X is oxygen or sulfur;

Y is methylene, oxygen or amino;

Z is oxygen or amino group; and

n is about 1 to 4.

In a preferred embodiment of the above mentioned compound the following are preferred;

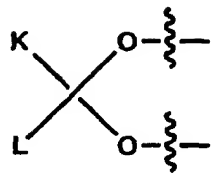
$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), halogen, thiol, alkylmercapto group of 1 to about 6 carbon atoms, heterocycles group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_1$ is a group of the formula OCO-$R_6$ wherein $R_6$ is alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, or lower alkoxy group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$) lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ are a group of formula OCO-$R_7$, wherein $R_7$ is 2-furanyl, lower alkyl group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:

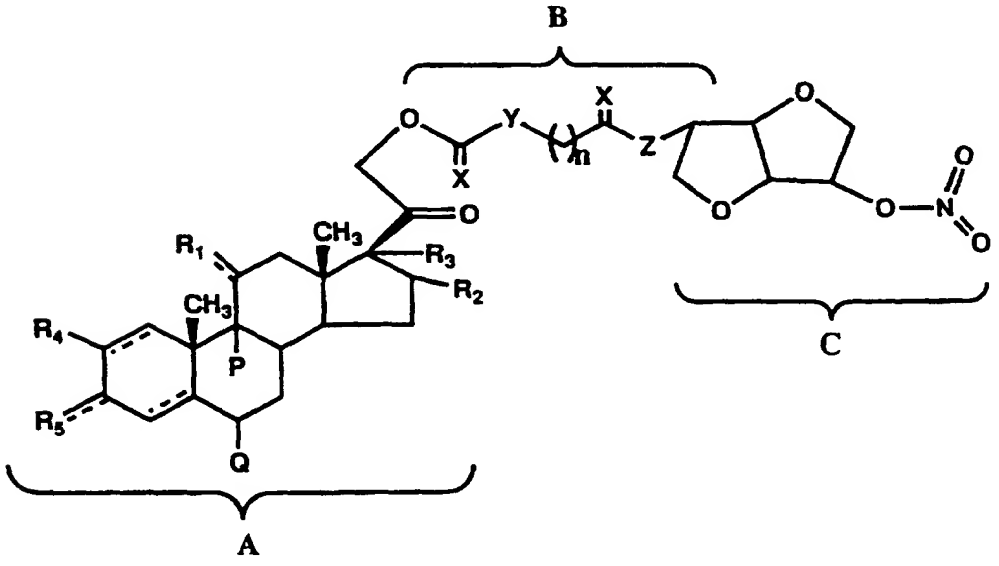


wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form an alicyclic hydrocarbon ring preferably containing a maximum of 8 carbon atoms or a heterocyclic ring preferably containing a maximum of 6 carbon atoms and 2 heteroatoms selected from nitrogen, oxygen or sulfur;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to about 6 carbon atoms.

The rest being as defined above.

Another embodiment is;



III

and wherein;

the dotted line in Formula **III** indicates a single or a double bond;

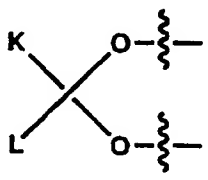
$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$) oxygen (ketone), lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro and haloalkyl radicals; or

$R_1$ is selected from the group of the formula $OCO-R_6$ wherein $R_6$ is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy group;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ are independently selected from the group of the formula $OCO-R_7$ wherein $R_7$ is 2-furanyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy group; or

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen,and lower alkyl; or optionally K

and L can form an alicyclic hydrocarbon or heterocyclic ring

$R_4$ is hydrogen or halogen;

$R_5$ is hydrogen, hydroxyl or oxygen ;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl;

X is oxygen or sulfur;

Y is methylene, oxygen or amino;

Z is oxygen or amino; and

n is about 1 to 4.

In a preferred embodiment of the above mentioned compound the following are preferred;

$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), halogen, thiol, alkylmercapto group of 1 to about 6 carbon atoms, heterocycles group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

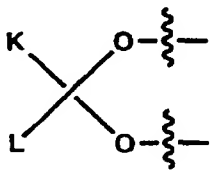
$R_1$ is a group of the formula OCO-$R_6$ wherein $R_6$ is alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group

of 2 to about 6 carbon atoms, or lower alkoxy group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ are a group of formula OCO-$R_7$ wherein $R_7$ is 2-furanyl, lower alkyl group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form an alicyclic hydrocarbon ring preferably containing a maximum of 8 carbon atoms or a heterocyclic ring preferably containing a maximum of 6 carbon atoms and 2 heteroatoms selected from nitrogen, oxygen or sulfur;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to about 6 carbon atoms.

The rest being as defined above.

While it may be possible for the preparations or compounds as defined above to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a preparation or a compound as defined above or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a preparation or a compound as defined above or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers, or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Formulations for administration by inhalation can be prepared for use as an aerosolized medicaments such as in manner recited in U.S. 5,458,135 and U.S. 5,447,150.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.01 to 500 mg/kg per day. The dose range for adult humans is generally from 0.1 mg to 1g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 0.05 mg to 250 mg, usually around 0.1 mg to 100 mg.

The compounds of formula (I) are preferably administered by inhalation, orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

As utilized herein, the term "lower alkyl", alone or in combination, means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like.

The term "lower alkenyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Examples of suitable alkenyl radicals include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "lower alkynyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-

1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethyl-butyn-1-yl radicals and the like.

The term "lower alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "alicyclic hydrocarbon" means an aliphatic radical in a ring with 3 to about 10 carbon atoms, and preferably from 3 to about 6 carbon atoms. Examples of suitable alicyclic radicals include cyclopropyl, cyclopropylenyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-ylenyl, cyclohexenyl and the like.

The term "heterocyclic radical" means a saturated or unsaturated cyclic hydrocarbon radical with 4 to about 10 carbon atoms, preferably about 5 to about 6; wherein 1 to about 3 carbon atoms are replaced by nitrogen, oxygen or sulfur. The "heterocyclic radical" may be fused to an aromatic hydrocarbon radical. Suitable examples include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazonlinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "prodrug" refers to a compound that is made more active in vivo.

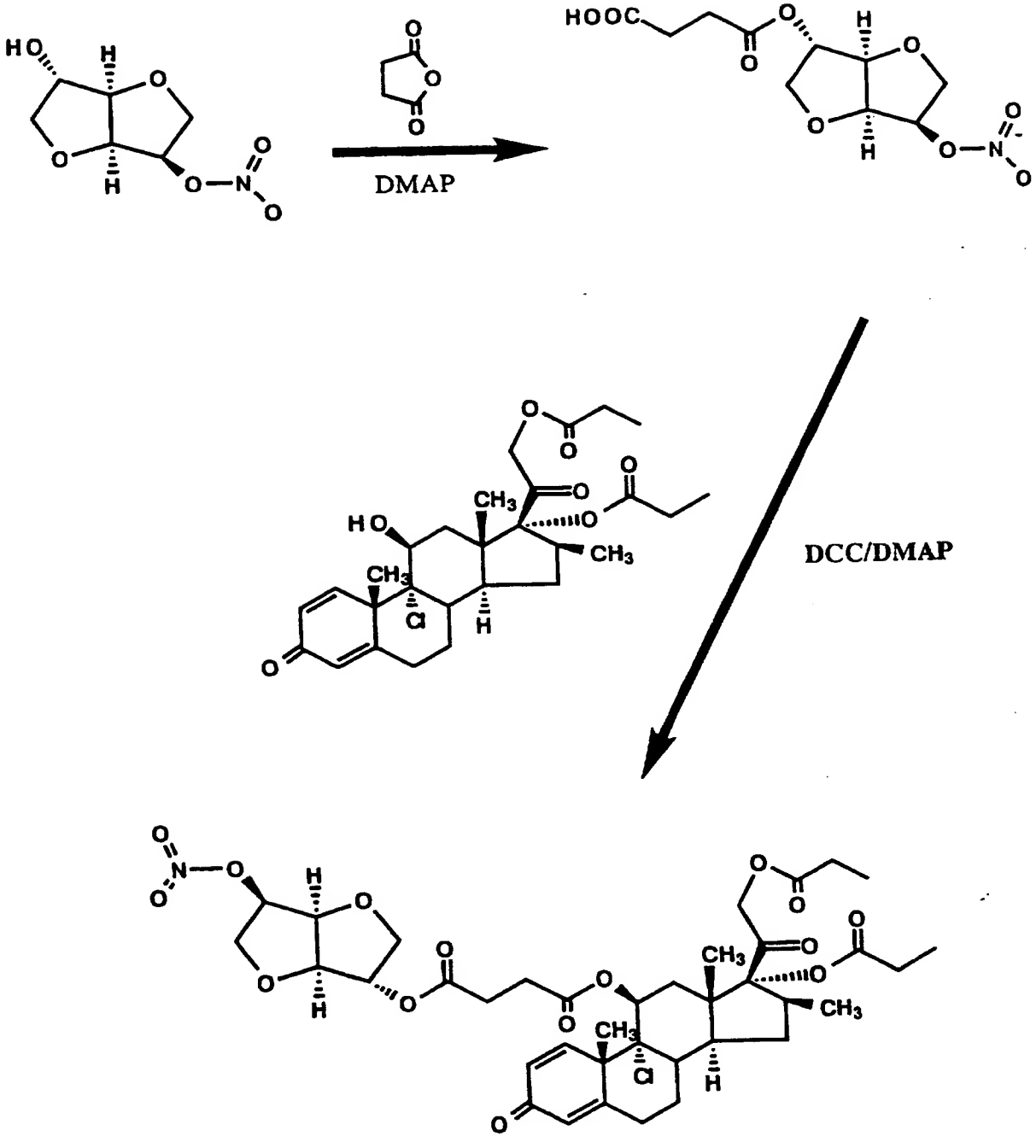
As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in this application are hereby incorporated by reference as if written herein.

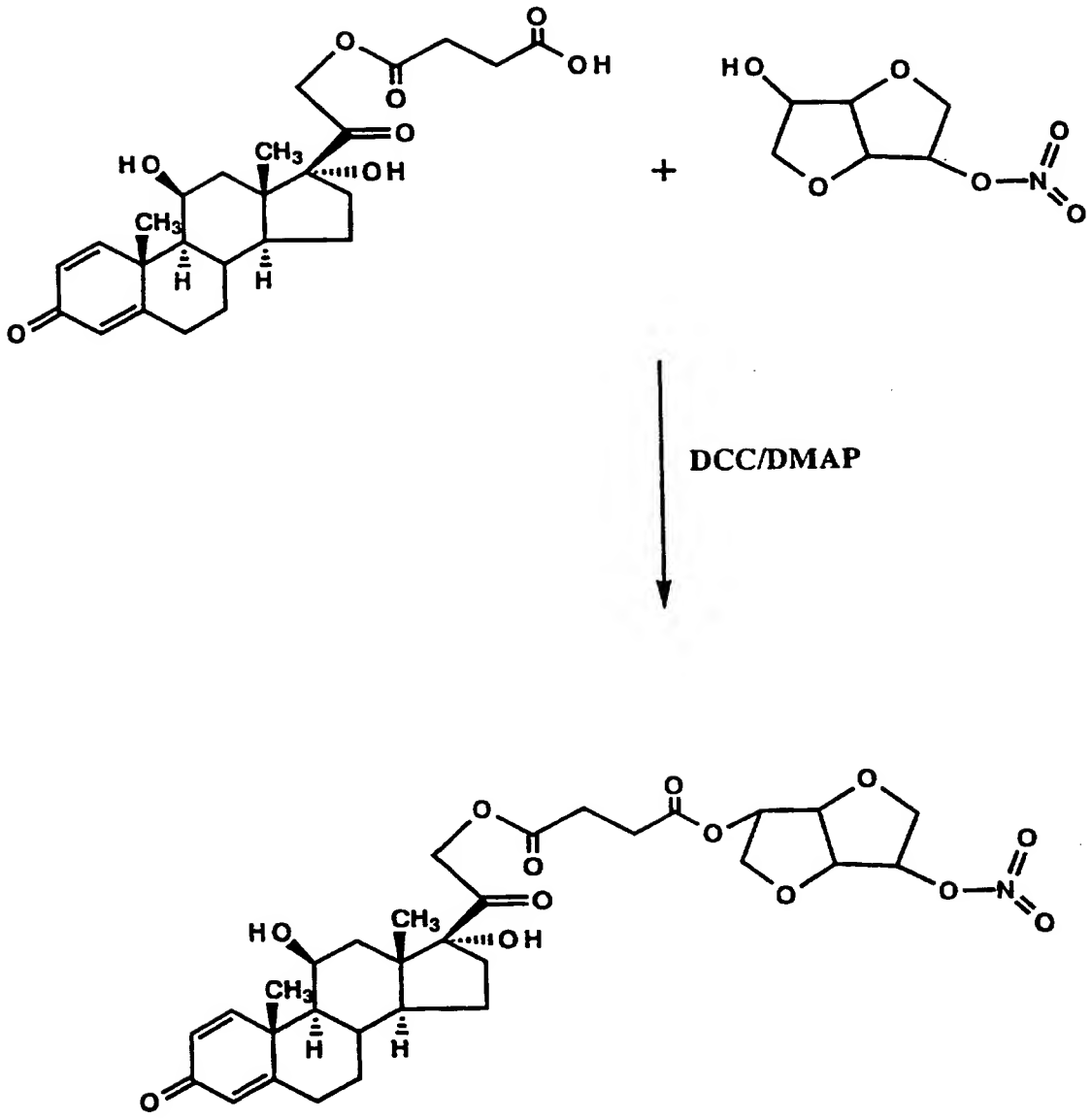
Starting materials used to make the present invention are commercially available such as from Sigma.

Four general synthetic schemes are outlined below for the compounds of the present invention.

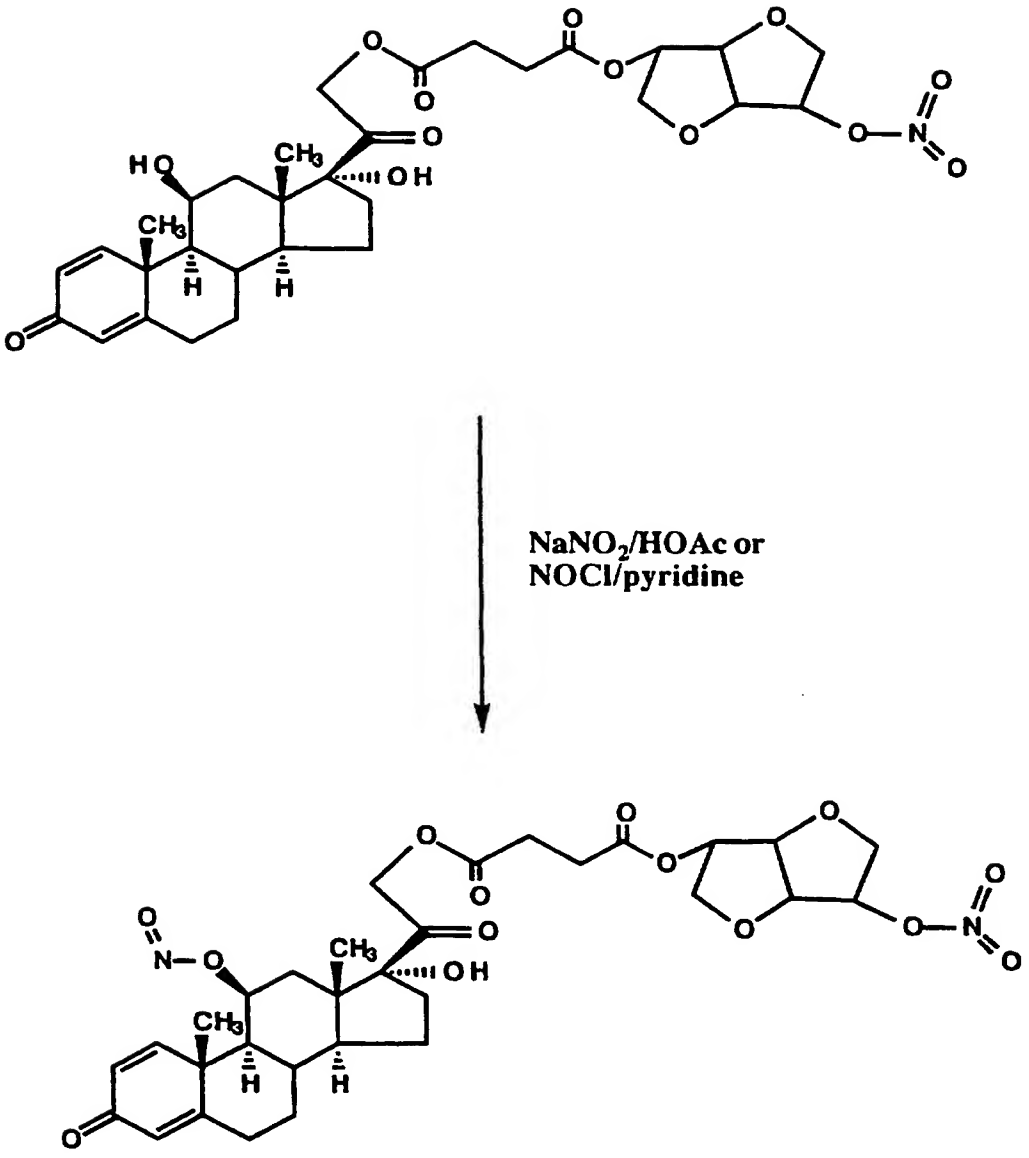
## SCHEME I



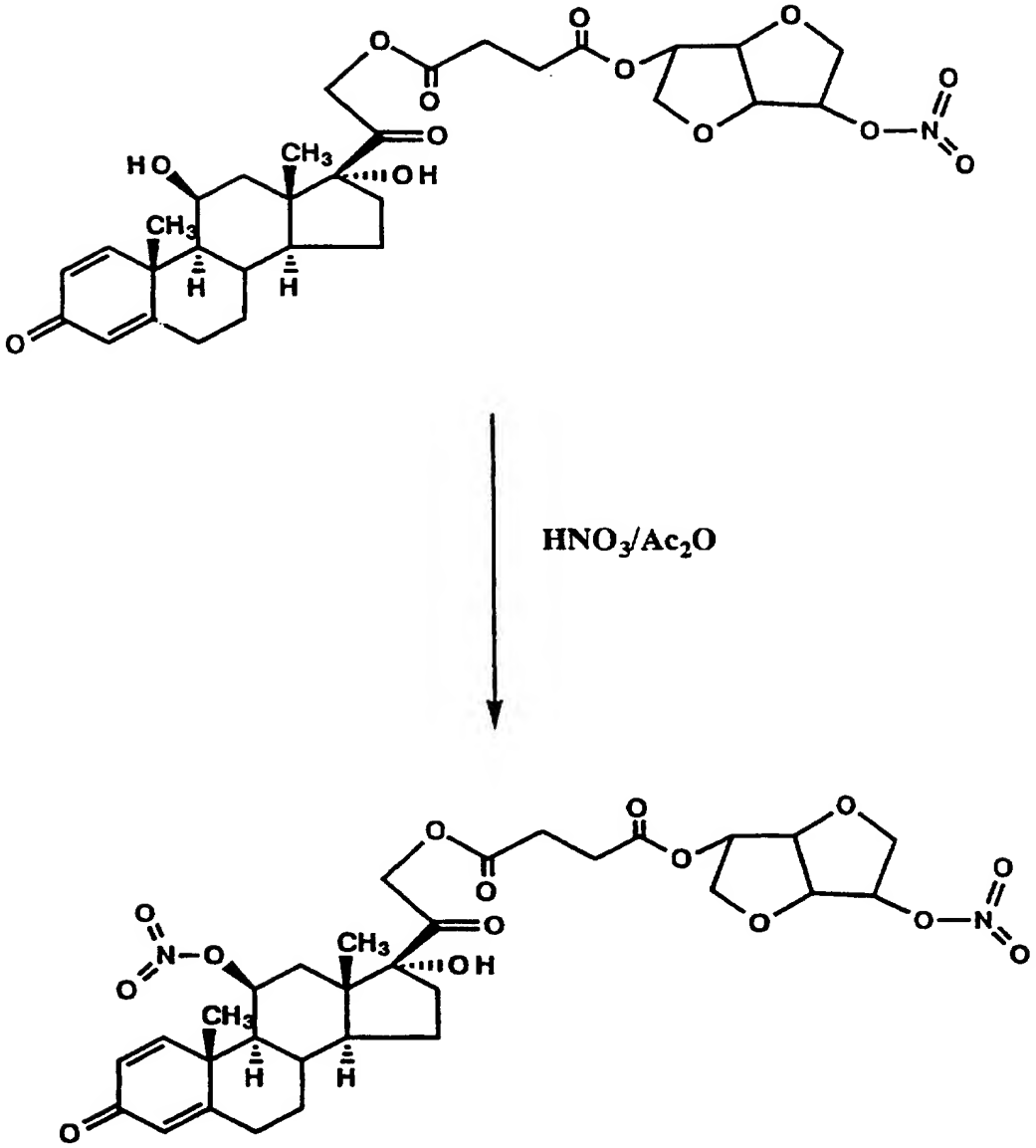
## SCHEME II



SCHEME III



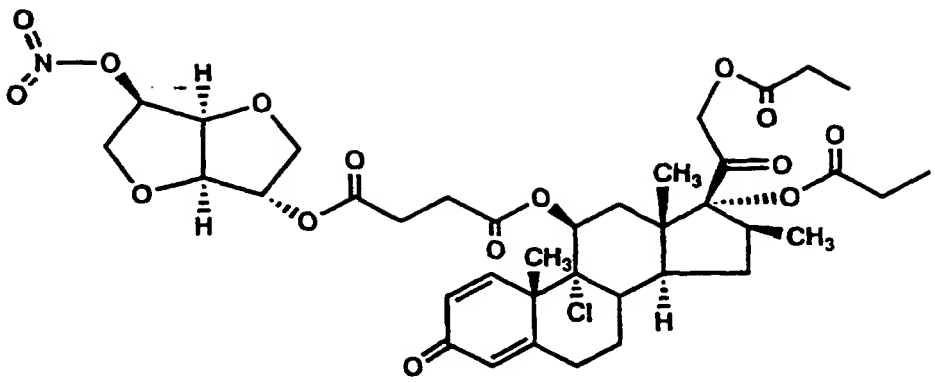
## SCHEME IV




It will be obvious to one skilled in the art to make modifications in the choice of starting materials and process conditions to make all of the invention compounds disclosesd herein.

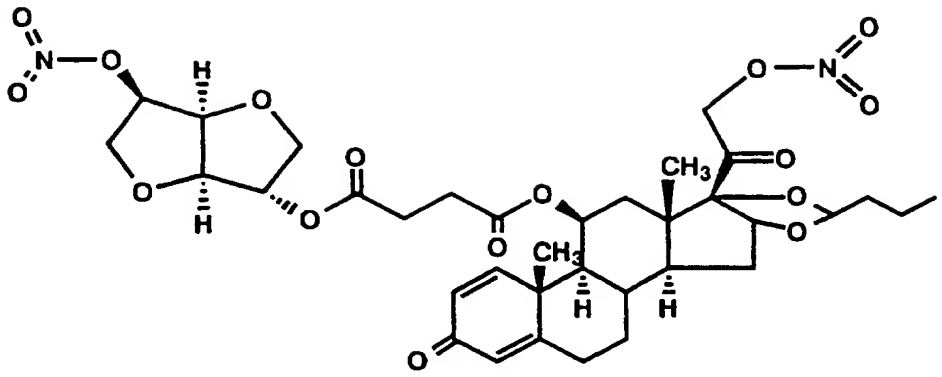
The invention is illustrated by the following examples.

EXAMPLE 1



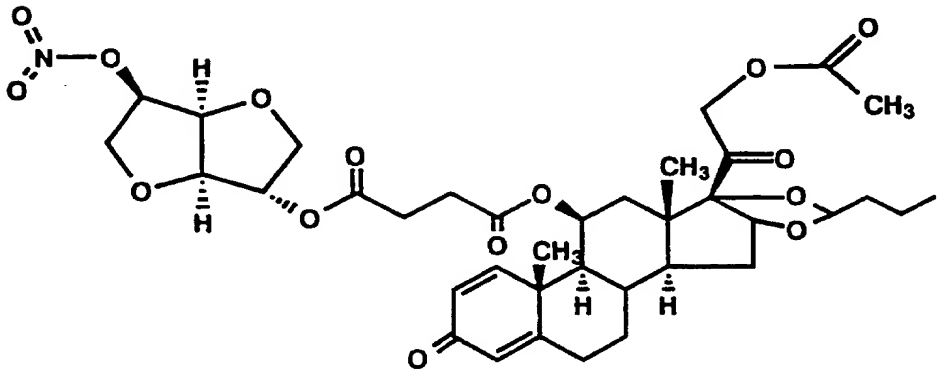
Isosorbide-5-nitrate (0.39 g; 2 mmoles) and 4-dimethylamino-pyridine (0.1 g) were added to a suspension of succinic anhydride (0.22 g; 2.2 mmoles) in dichloromethane (25 ml) with stirring. The clear reaction mixture was then stirred at room temperature overnight. 9α-chloro-16β-methylprednisolone-17,21-dipropionate (1 g; 1.9 mmoles), dicyclohexylcarbodiimide (0.45 g; 2.2 mmoles) and 4-dimethylaminopyridine (0.1 g) in dichloromethane (100 ml) were added and the mixture was stirred for another day. The solid was filtered and the filtrate was taken down to dryness. The residue was purified on a Waters μBondapak column (30 cm X 5 cm) using a linear gradient of 25-75% acetonitrile/water/trifluoroacetic acid. The desired fractions were collected and lyophylized to give 400 mg of white material. FAB-MS: $(M+Li)^+$ = 800; $^1$H-NMR ($CDCl_3$) δ 0.88 (s, 3H, $CH_3$(C-18)), 1.1-1.2 (m, 6H, $2\underline{CH_3}$-$CH_2$), 1.35 (d, 3H, CH-$\underline{CH_3}$), 1.55 (s, 3H, $CH_3$(C-19)), 2.35-2.5 (m, 4H, $2CH_3$-$\underline{CH_2}$), 2.51-2.7 (m, 4H, CO-$(CH_2)_2$-CO), 3.85-4.05 (m, 4H, isosorbide), 4.25 and 4.7 (2d, 2H, CO-$CH_2$-O), 4.5 (m, 1H, isosorbide) , 4.98 (m, 1H, isosorbide), 5.38 (d, 1H, CH(C-11)), 5.62 (m, 1H, isosorbide), (6.1 (s, 1H, CH(C-4)), 6.35 (d, 1H, CH(C-2)), 6.85 (d, 1H, CH(C-1)).

EXAMPLE 2



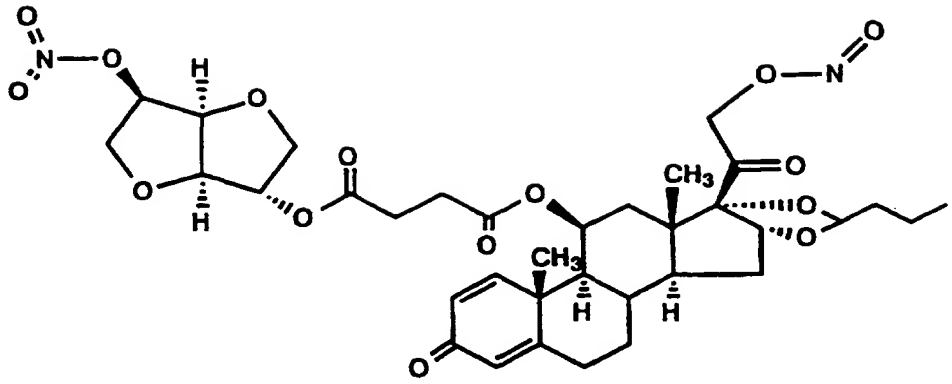
The title compound is prepared from budesonide-21-nitrate in the same manner as described for EXAMPLE 1.

EXAMPLE 3



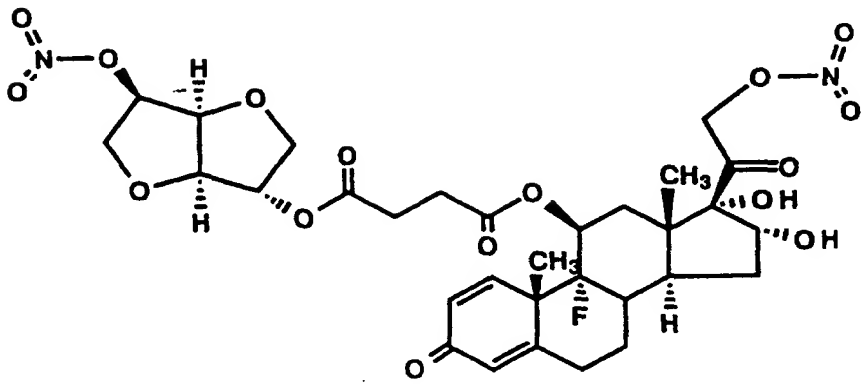
The title compound is prepared from budesonide-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 4



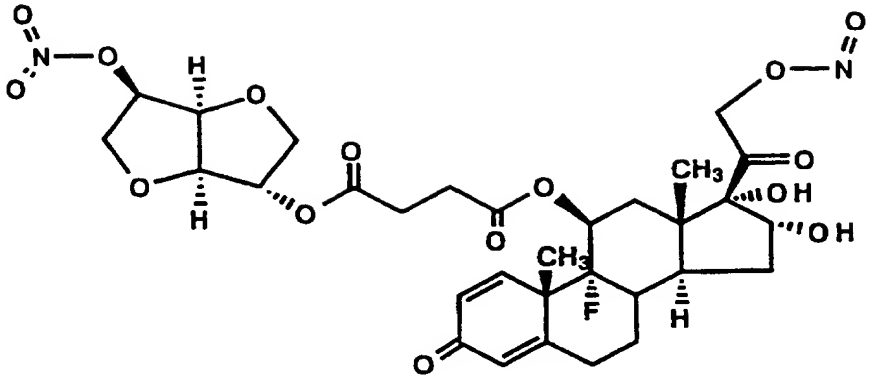
The title compound is prepared from budesonide-21-nitrite in the same manner as described for EXAMPLE 1.

EXAMPLE 5



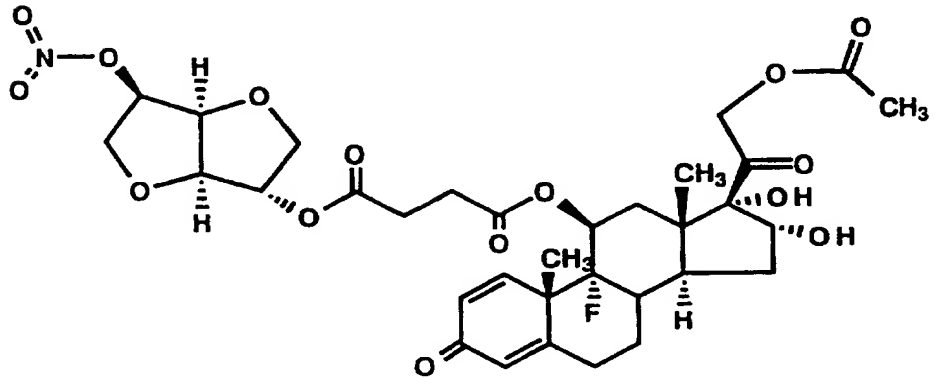
The title compound is prepared from triamcinolone-21-nitrate in the same manner as described for EXAMPLE 1.

EXAMPLE 6



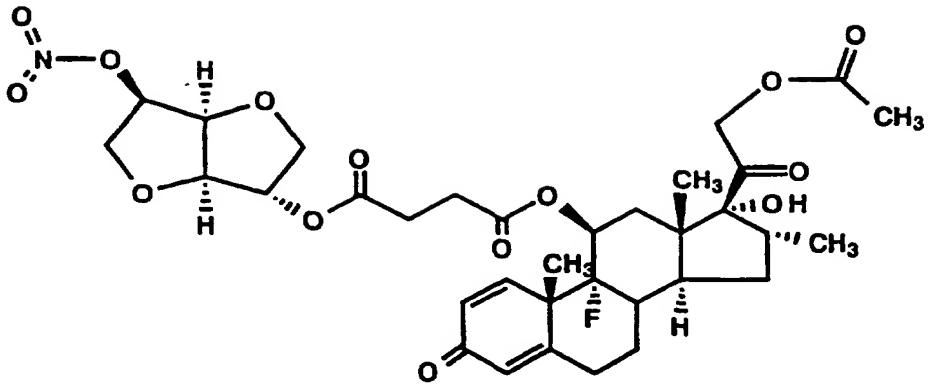
The title compound is prepared from triamcinolone-21-nitrite in the same manner as described for EXAMPLE 1.

EXAMPLE 7



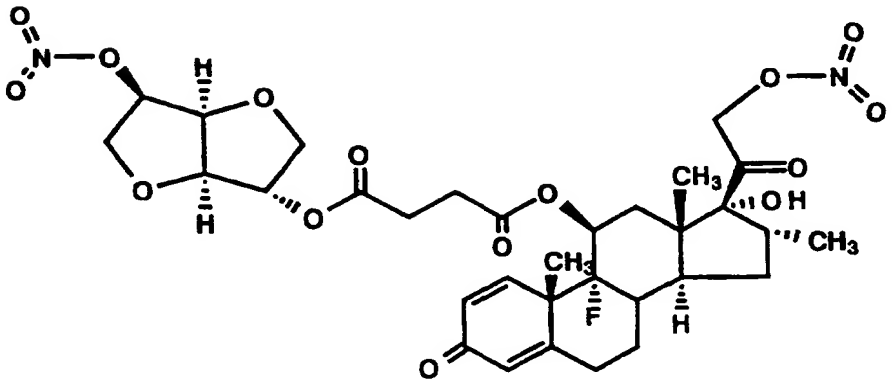
The title compound is prepared from triamcinolone-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 8



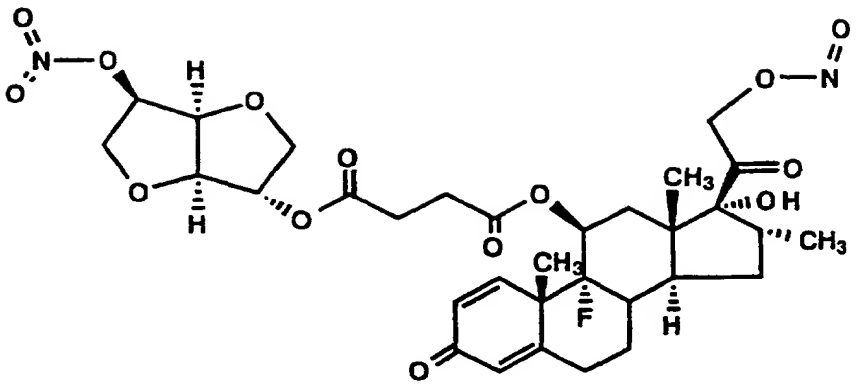
The title compound is prepared from dexamethasone-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 9



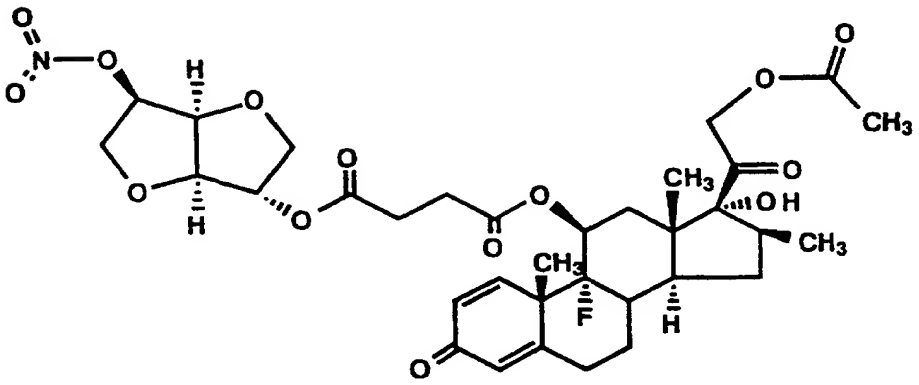
The title compound is prepared from dexamethasone-21-nitrate in the same manner as described for EXAMPLE 1.

EXAMPLE 10



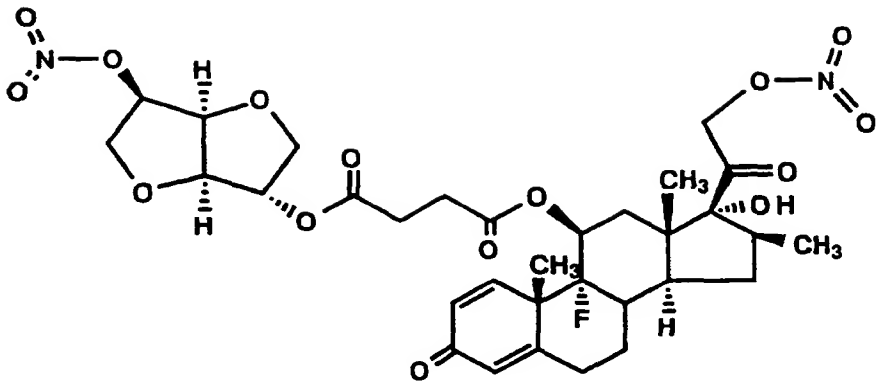
The title compound is prepared from dexamethasone-21-nitrite in the same manner as described for EXAMPLE 1.

EXAMPLE 11



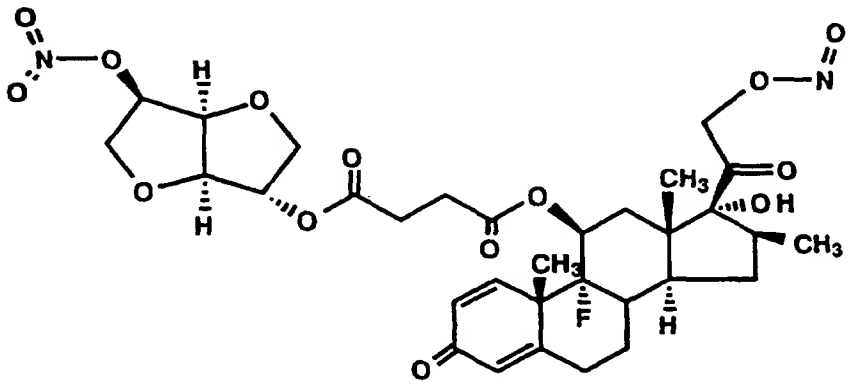
The title compound is prepared from betamethasone-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 12



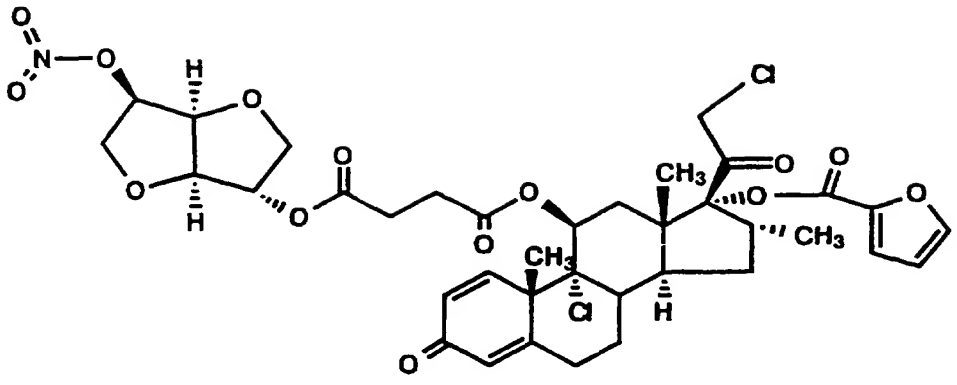
The title compound is prepared from betamethasone-21-nitrate in the same manner as described for EXAMPLE 1.

EXAMPLE 13



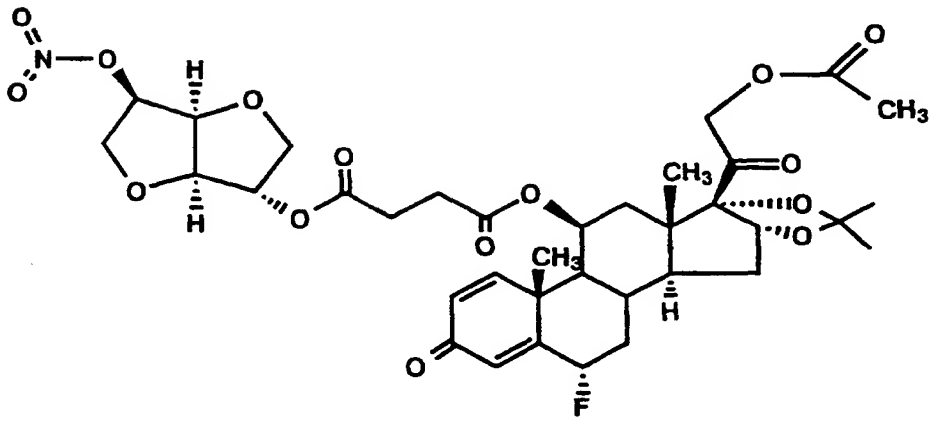
The title compound is prepared from betamethasone-21-nitrite in the same manner as described for EXAMPLE 1

EXAMPLE 14



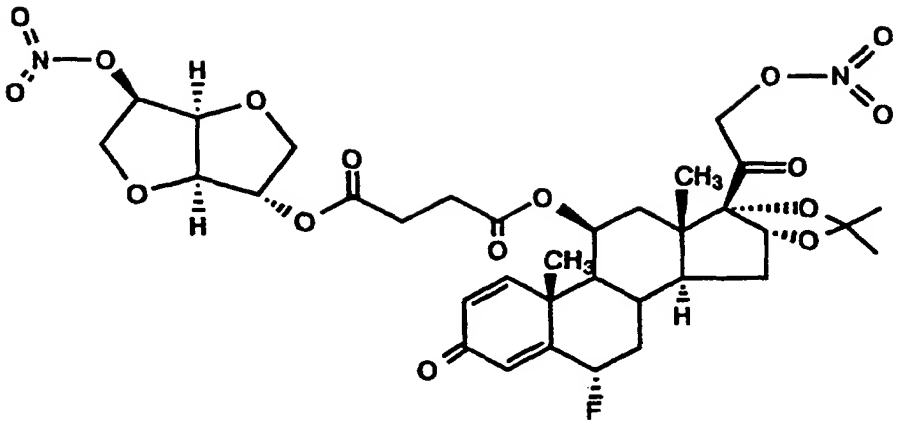
The title compound is prepared from mometasone furoate in the same manner as described for EXAMPLE 1.

EXAMPLE 15



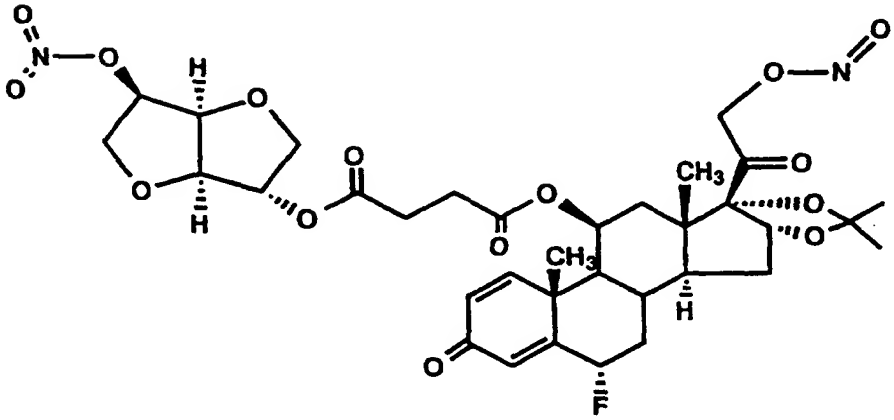
The title compound is prepared from flunisolide-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 16



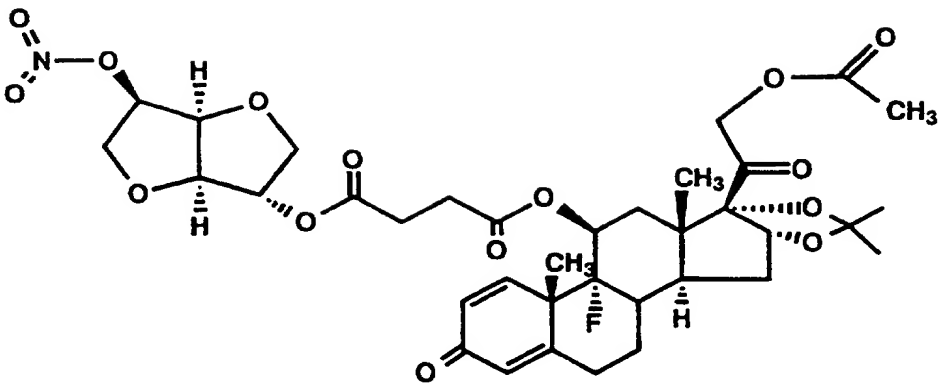
The title compound is prepared from flunisolide-21-nitrate in the same manner as described for EXAMPLE 1.

EXAMPLE 17



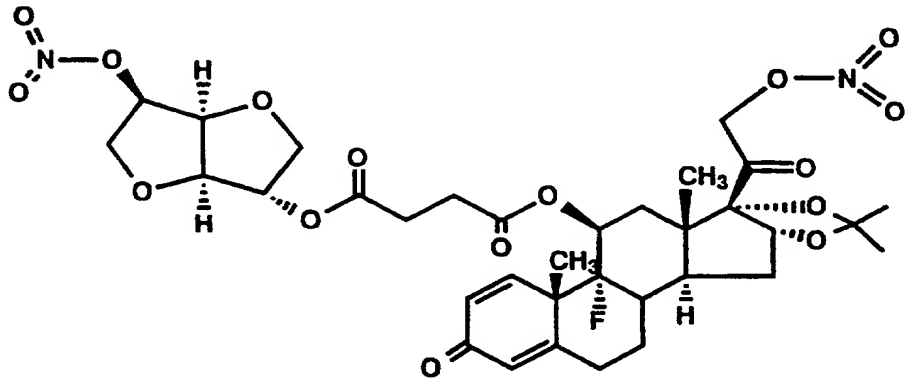
The title compound is prepared from flunisolide-21-nitrite in the same manner as described for EXAMPLE 1.

EXAMPLE 18



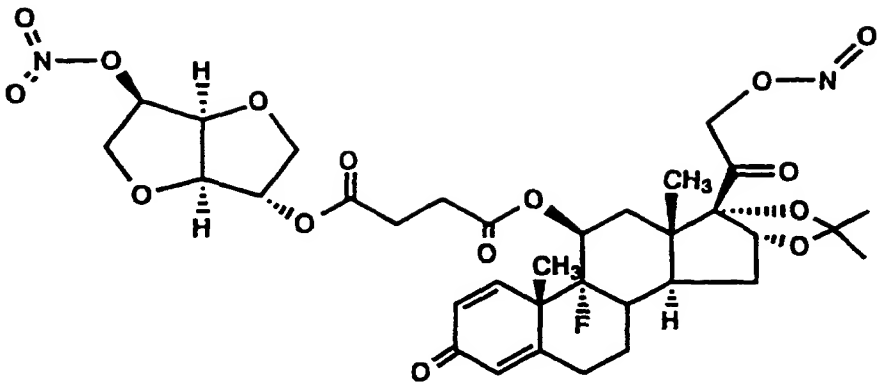
The title compound is prepared from triamcinolone-21-acetate acetonide in the same manner as described for EXAMPLE 1.

EXAMPLE 19



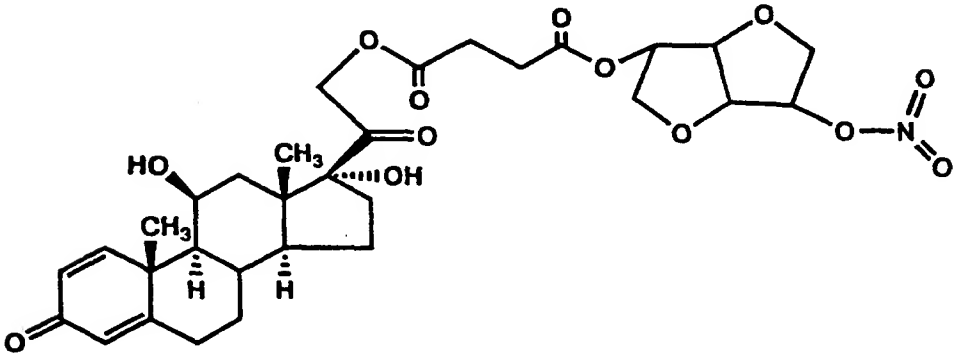
The title compound is prepared from triamcinolone-21-nitrate acetonide in the same manner as described for EXAMPLE 1.

EXAMPLE 20



The title compound is prepared from triamcinolone-21-nitrite acetonide in the same manner as described for EXAMPLE 1.

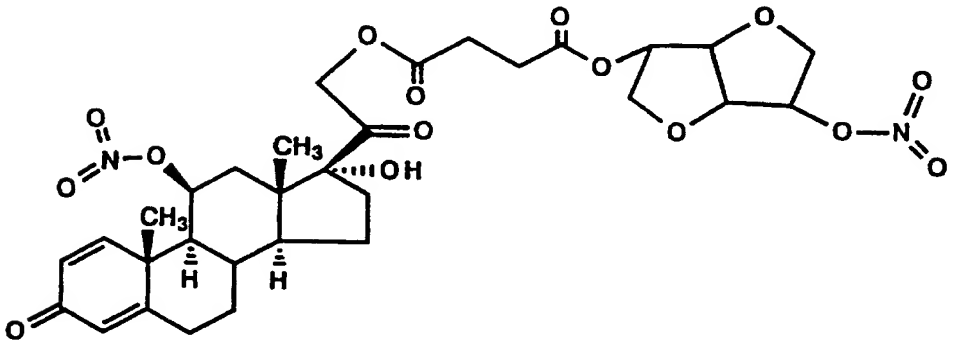
EXAMPLE 21



Prednisolone-21-hemisuccinate (0.47 g; 1 mmole), isosorbide-5-mononitrate (0.9 g; 5 mmoles) and DMAP (100 mg) were dissolved in chloroform (20 ml) and dimethylformamide (2 ml). To this solution, dicyclohexylcarbodiimide (0.26 g; 1.3 mmoles) in chloroform (5 ml) was added with stirring. The reaction mixture was stirred overnight and filtered. The filtrate was taken down to dryness and the residue was purified on a Waters µBondapak column (30 cm X 5 cm) using a linear gradient of 25-75% acetonitrile/water/ trifluoroacetic

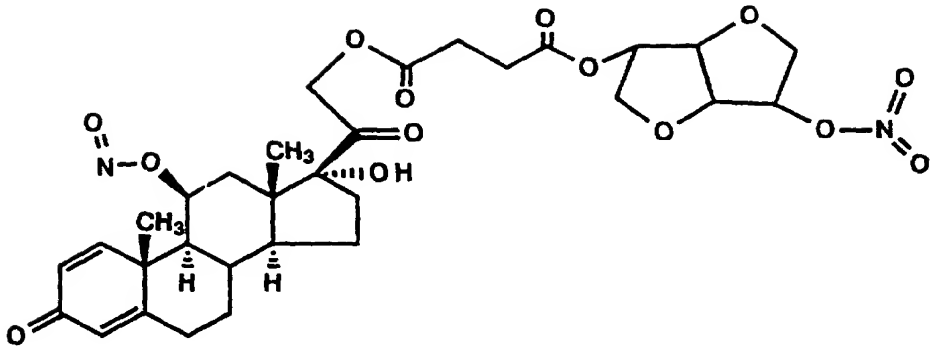
acid. The desired fractions were collected and lyophylized to give mg of white material. FAB-MS: $(M+Li)^+$ =640; $^1$H-NMR ($CDCl_3$) δ 0.97 (s, 3H, $CH_3$(C-18)), 1.47 (s, 3H, $CH_3$(C-19)), 2.6-2.85 (m, 4H, CO-$(CH_2)_2$-CO), 3.85-4.1 (m, 4H, isosorbide), 4.5 and 5.0 (m, 2H, isosorbide), 4.5 (d, 1H, CH(C-11)), 6.06 (s, 1H, CH(C-4)), 6.35 (d, 1H, CH(C-2)), 7.37 (d, 1H, CH(C-1)).

EXAMPLE 22



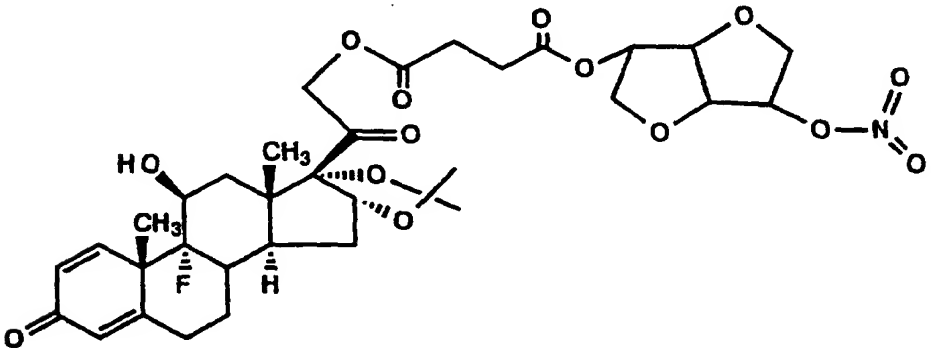
Fuming nitric acid (1 ml; d = 1.49) and acetic anhydride (2.5 ml) are combined at -10 $^0$C. To this solution, a pre-cooled suspension of EXAMPLE 21 (1 mmole) in chloroform (20 ml) is added dropwise with stirring. The mixture is stirred for 4 h at 0 $^0$C and poured into ice water (50 ml). The organic phase is separated and washed with water, saturated sodium bicarbonate solution and water. After drying over sodium sulfate overnight, the solid is filtered and the filtrate is taken down to dryness. The residue is purified on a Waters μBondapak column (30 cm X 5 cm) using a linear gradient of 25-75% acetonitrile/water/trifluoroacetic acid.

EXAMPLE 23



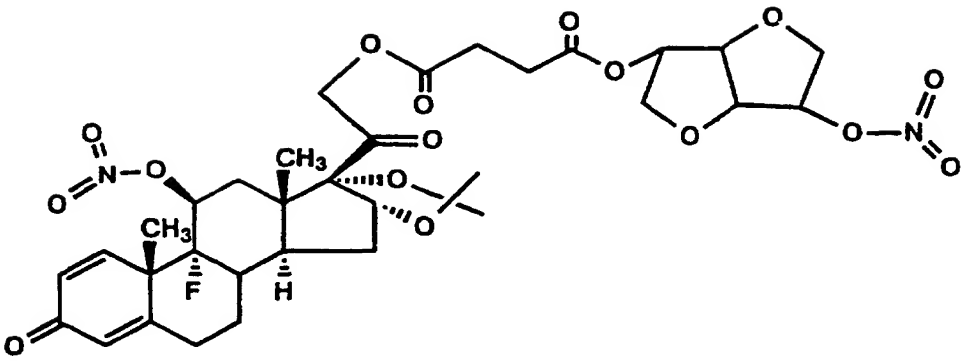
A solution of EXAMPLE 21 (0.02 mmoles) in acetic acid (1 ml) is warmed up to 55 $^{0}C$ and treated with solid sodium nitrite (0.007 g; 0.1 mmole) for 30 seconds. The product is precipitated by addition of ice water (5 ml) and filtered. The solid is washed with water and dried over $P_2O_5$ in vacuo to give a white solid material.

EXAMPLE 24



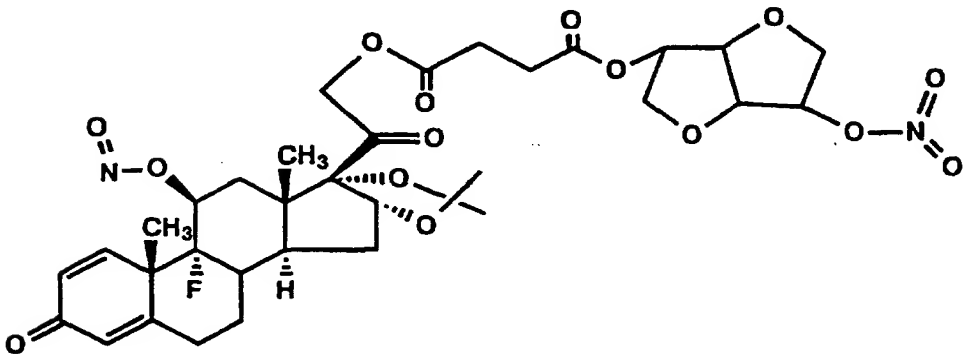
Triamcinolone-21-hemisuccinate acetonide (1 mmole), isosorbide-5-mononitrate (5 mmoles) and DMAP (100 mg) are dissolved in chloroform (20 ml) and dimethylformamide (2 ml). To this solution, dicyclohexylcarbodiimide (1.3 mmoles) in chloroform (5 ml) is added with stirring. The reaction mixture is stirred overnight and worked up as described for EXAMPLE 21 to give the title compound.

EXAMPLE 25



The title compound is prepared from EXAMPLE 24 in the same manner as described in the preparation of EXAMPLE 22.

EXAMPLE 26



The title compound is prepared from EXAMPLE 24 in the same manner as described in the preparation of EXAMPLE 23.

## Biological Data

The subject compounds have been found to be nitric oxide donors while maintaining their steroid activities and possess useful pharmacological properties as demonstrated by EXAMPLE 1 and EXAMPLE 21 in the *in vitro* smooth relaxant activity assay: The test compound and the parent steroid were examined for the ability to relax smooth muscle. The rat aortic ring assay was utilized as a bioassay to measure the relaxant activity. The rings were precontracted with phenylephrine (0.3uM) and subsequently compounds were added to the tissue bath in the presence of cysteine (Cys) and $N^G$-L-nitroarginine methyl ester (L-NAME):

**A. *In vitro* smooth muscle relaxant activity assay in the presence of Cys and L-NAME:**

| Compound | Relaxation, $EC_{50}$ [uM] |
|---|---|
| Beclomethasone-dipropionate | 100 |
| Example 1 | > 10 |
| Example 21 | 3 |

These data indicate that these compounds have smooth muscle relaxant activity, while the control compound Beclomethasone-dipropionate did not show any effect.

**B. *In vitro* inhibiton of prostaglandin $E_2$ ($PGE_2$) synthesis assay:** Human fetal fibroblast cells were treated with IL-1 for 16 hours and prostaglandin $E_2$ was measured by an ELISA. Compounds were given at the time of addition of IL-1. This assay provides an in vitro assessment of the compound to block the induction of the proinflammatory agent prostaglandin $E_2$ ($PGE_2$):

| Treatment | $PGE_2$ (ng) |
|---|---|
| Basal | 0.6 |
| IL-1 | 9.4 |
| IL-1 and Dexamethasone(10uM) | 0.6 |
| IL-1 and Example 1(10uM) | 0.5 |
| IL-1 and Example 21 (10uM) | 0.4 |

These data indicate that the steroids with the modifications for the generation of nitric oxide are effective at inhibiting the increase in $PGE_2$ and maintain the glucocorticoid action of the prevention of prostaglandin formation.

WHAT IS CLAIMED IS:

1. A compound having the formula:

**A-B-C** **1**

wherein;

**A** is a hydroxyl containing steroidal hormone;
**C** is an nitrite or nitrate containing compound; and
**B** is lower alkyl, lower alkenyl, lower alkynyl.

2. The compound as recited in Claim 1 wherein;

A is selected from the group consisting of

21-Acetoxypregnenolone, 70
Alclometasone, 213
Algestone, 229
Amcinonide, 398
Beclomethasone, 1029
Betamethasone, 1202
Budesonide, 1455
Chlorprednisone, 2157
Clobetasol, 2361
Clocortolone, 2368
Cloprednol, 2396
Corticosterone, 2532
Cortisone, 2533
Corticazol, 2536
Hydrocortisone Phosphate, 4712
Hydrocortisone 21-Sodium Succinate, 4713
Hydrocortisone terbutate, 4714
Maziipredone, 5644
Medrysone, 5679
Meprednisone, 5750
Methylprednisolone, 6028
Mometasone Furoate, 6151
Paramethasone, 6977
Prednicarbate, 7177
Prednisolone 21-Diethylaminoacetate, 7720
Prednisolone Sodium Phosphate, 7721

Deflazacort, 2852

Desonide, 2908

Dexamethasone, 2922

Diflorasone, 3126
Diflucortolone, 3129

Difluprednate, 3134

Enoxolone, 3543
Fluazacort,4048
Flucloronide, 4053
Flumethasone, 4066
Flunisolide, 4071

Flucinolone Acetonide, 4076
Fluocinonide, 4077
Fluocortin Butyl, 4078
Fluocortolone, 4079

Fluorometholone, 4104

Fluperolone, Acetate, 4118

Fluprednidene Acetate, 4115
Fluprednisolone, 4119
Flurandrenolide, 4112
Formocortal, 4156
Halcinonide, 4504
Halometasone, 4510
Haloprednone Acetate, 4512
Hydrocortamate, 4709
Hydrocortisone, 4710
and
Fluticasone.

Prednisolone Sodium Succinate, 7722
Prednisolone Sodium 21-m-Sulfo-benzoate, 7723
Prednisolone 21-Stearoylglycolate, 7724

Prednisolone Terbutate, 7725
Prednisolone 21-Trimethylacetate, 7726

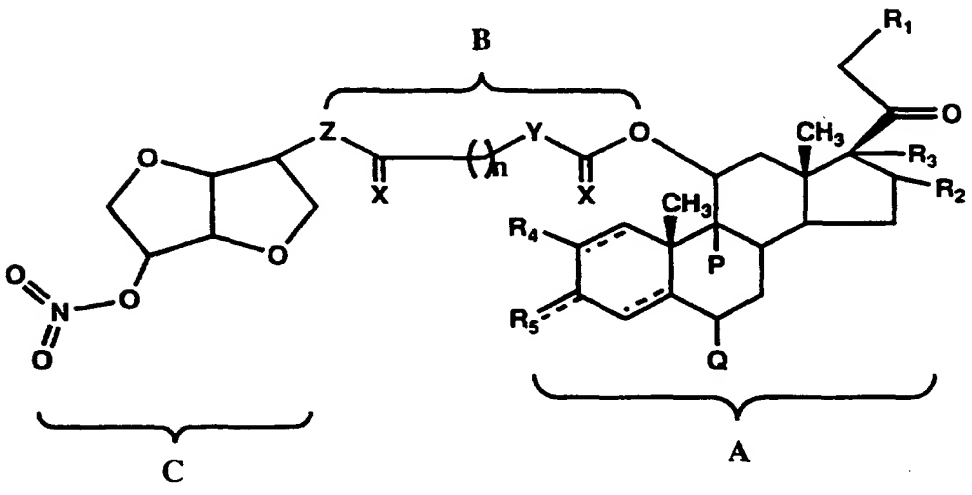
Prednisone, 7727
Prednival, 7728
Prednylidene, 7729
Prednylidene 21-Diethylaminoacetate, 7730

Tixocortol, 9408
Triamcinolonek 9511
Triamcinolene Acetonide, 9512
Triamcinolone Benetonide, 9513
Triamcinolone Hexacetonide, 9514

3. The compound as recited in Claim 1 wherein C is glyceryl nitrate, amylnitrite, isosorbide mononitrate, isosorbide dinitrate, mannitol nitrate, pentaerythritol nitrate or propatyl nitrate.

4. The compound as recited in Claim 1 wherein B is attached to **A** through the hydroxyl of A via an amide, ester, carbamate or carbonate linkage and **C** through an amino or a hydroxyl group.

5. A compound having the formula:




II

wherein;

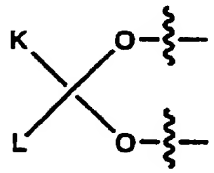
the dotted lines in Formula **II** indicate a single or a double bond;

$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), halogen, thiol, alkylmercapto, heterocycles, lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_1$ is of formula OCO-$R_6$ wherein $R_6$ is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy group;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy and a group of formula OCO-$R_7$ wherein $R_7$ is 2-furanyl, lower alkyl or lower alkoxy group, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals;or

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl, or optionally K and L can form an alicyclic hydrocarbon or heterocyclic ring;

$R_4$ is hydrogen or halogen;

$R_5$ is hydrogen, hydroxyl, or oxygen;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group;

X is oxygen or sulfur;

Y is methylene, oxygen or amino;

Z is oxygen or amino group; and

n is about 1 to 4.

6. The compound as recited in Claim 5 wherein

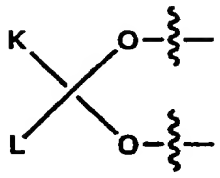
$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), halogen, thiol, alkylmercapto group of 1 to about 6 carbon atoms, heterocycles group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_1$ is a group of the formula OCO-$R_6$ wherein $R_6$ is an alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, or lower alkoxy group group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$) lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ are a group of formula OCO-$R_7$ wherein $R_7$ is 2-furanyl, lower alkyl group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

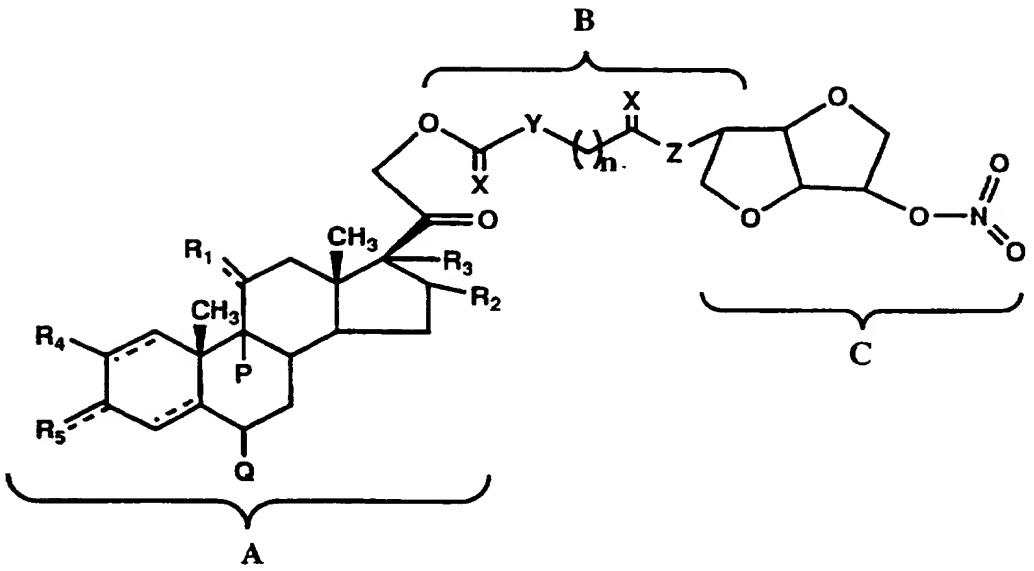
$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form an alicyclic hydrocarbon ring preferably containing a maximum of 8 carbon atoms or a heterocyclic ring preferably containing a maximum of 6 carbon atoms and 2 heteroatoms selected from nitrogen, oxygen or sulfur; and

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to about 6 carbon atoms.

7. A compound having the formula:




III

and wherein;

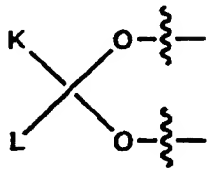
the dotted line in Formula III indicates a single or a double bond;

$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$),oxygen (ketone), lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro and haloalkyl radicals; a group of formula OCO-$R_6$ wherein $R_6$ is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy group;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy and a group of the formula OCO-R7 wherein R7 is 2-furanyl, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy group, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy,

amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:




wherein, K and L are selected from the group consisting of hydrogen,and lower alkyl; or optionally K and L can form an alicyclic hydrocarbon or heterocyclic ring

$R_4$ is hydrogen or halogen;

$R_5$ is hydrogen, hydroxyl or oxygen ;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl;

X is oxygen or sulfur;

Y is methylene, oxygen or amino;

Z is oxygen or amino; and

n is about 1 to 4.

8. The compound as recited in Claim 7 wherein;

$R_1$ is selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$), halogen, thiol, alkylmercapto group of 1 to about 6 carbon atoms, heterocycles group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8

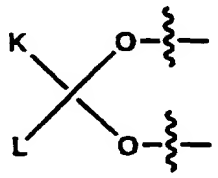
carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitrile, carboxyl and haloalkyl radicals; or

$R_1$ is a group of the formula OCO-$R_6$ wherein $R_6$ is alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, or lower alkoxy group group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ are independently selected from the group consisting of hydrogen, hydroxyl, nitrite ester (ONO), nitrate ester ($ONO_2$) lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

$R_2$ and $R_3$ are a group of formula OCO-$R_7$ wherein $R_7$ is 2-furanyl, lower alkyl group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

$R_2$ and $R_3$ may optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form an alicyclic hydrocarbon ring preferably containing a maximum of 8 carbon atoms or a heterocyclic ring preferably containing a maximum of 6 carbon atoms and 2 heteroatoms selected from nitrogen, oxygen or sulfur; and

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to about 6 carbon atoms.

9. A pharmaceutical composition comprising a compound as recited in Claims 1, 2, 3, 4, 5 or 6 and together with a pharmaceutically acceptable carrier.

10. A method of treating a patient with inflammation by administering a therapeutically effective amount of the compound as recited in Claims 1, 2, 3, 4 ,5 or 6.

11. The method of Claim 8 wherein said patient also has undesired smooth muscle contractions.

# INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 97/06373

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J41/00 A61K31/57 C07J71/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US 3 183 252 A (P. CRABBÉ ET AL) 11 May 1965<br>see example XIV, compounds 52,54, example XV, compounds 74,76,78 and example XVI, compound 88<br>--- | 1,9<br>1-9 |
| Y | DE 22 22 491 A (RICHTER GEDEON GYAR RT) 16 November 1972<br>see examples 3-5,9,10<br>--- | 1-9 |
| Y | ARZNEIMITTEL FORSCHUNG DRUG RESEARCH., vol. 37, no. 6, 1987, AULENDORF DE, pages 692-698, XP002035557<br>M. LEITOLD ET AL: "Untersuchungen zur Pharmakologie und Pharmakokinetik von Glycerol-2-nitrat"<br>see the whole document<br>---<br>-/-- | 1-9 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 July 1997 | -4 -08- 1997 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | Authorized officer<br>Watchorn, P |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 41, no. 6, June 1993, pages 1100-1110, XP000611905 HAYASHI H ET AL: "1,4:3,6-DIANHYDROHEXITOL NITRATE DERIVATIVES. II. 1) SYNTHESIS AND ANTIANGINAL ACTIVITY OF ARYL- OR ARYLCARBONYLPIPERAZINE DERIVATIVES 2)" see the whole document --- | 1-9 |
| Y | PHARM. CHEM. J. (KHIM. FARM. ZH.), vol. 14, no. 12, 1980, pages 60-62, XP002035558 BAYUNOVA ET AL: see the whole document --- | 1-9 |
| Y | CHEMICAL ABSTRACTS, vol. 70, no. 9, 3 March 1969 Columbus, Ohio, US; abstract no. 38001, T. MIKI ET AL: "Antiinflammatory Steroid Derivatives" page 380; column 2; XP002035559 see abstract & JP 68 003 780 A (TAKEDA CHEMICAL INDSUTRIES LTD) 12 February 1968 --- | 1-9 |
| Y | US 2 990 401 A (S. BERNSTEIN ET AL) 27 June 1961 see example 18 --- | 1-9 |
| A | US 3 002 010 A (V ORIGONI ET AL) 26 September 1961 see column 2, paragraph 2 ----- | 1-9 |

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/06373

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 10 and 11 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible] Application No
PC[illegible] 97/06373

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| DE 2222491 A | 16-11-72 | AT 316767 A,B | 15-06-74 |
| | | AT 331428 A,B | 25-08-76 |
| | | AU 469581 B | 19-02-76 |
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| | | SE 385590 B | 12-07-76 |
| | | SE 7503290 A | 21-03-75 |
| US 2990401 A | 27-06-61 | NONE | |
| US 3002010 A | 26-09-61 | NONE | |